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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,215	05/17/2001	Peter Huub Gerard Maria Kirchholtes	D/98409 US	7592

7590 02/02/2004

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EXAMINER	
JIANG, SHAOJIA A	
ART UNIT	**PAPER NUMBER**
1617	

DATE ~~MAILED:~~ 02/02/2004

Restart

Please find below and/or attached an Office communication concerning this application or proceeding.

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7590 06/18/2003

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JIANG, SHAOJIA A	
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DATE ~~MAILED: 06/18/2003~~
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Office Action Summary	Application No. 09/787,215	Applicant(s) KIRCHHOLTES ET AL.	
	Examiner Shaojia A. Jiang	Art Unit 1617	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-11 and 13-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-11 and 13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 31, 2003 has been entered in Paper No. 15.

This Office Action is a response to Applicant's request for continued examination (RCE) filed March 31, 2003 in Paper No.15, and amendment and response to the Final Office Action (mailed October 2, 2002), filed March 31, 2003 in Paper No. 16 wherein claims 1-7, 9-11, and 13-18 have been amended, and claims 19-20 are newly submitted. Currently, claims 1-7, 9-11,13-18 and 19-20 are pending in this application.

Claims 1-7, 9-11,13-18 and 19-20 are examined on the merits herein.

Applicant's declaration of Martinus A. Lunenburg submitted March 31, 2003 in Paper No. 17 under 37 CFR 1.132, is acknowledged and will be further discussed below.

Applicant's amendment (amending claim 9, 12-15) with respect to the objection of claims 9, 12-15 made under 37 CFR 1.75 (c) for improper dependent for inherent property of the compositions of record stated in the Office Action dated October 2, 2002

have been fully considered and are found persuasive. Therefore, this objection is withdrawn.

Claim Objection

Claims 17-18 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, of record in the previous Office Action October 2, 2002, in which claims 17-18 are objected for failing further limited claim 14 since the dependent claims 17-18 are broader in scope than claim 14.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 7 and 9 as amended now are rejected under 35 U.S.C. 102(b) as being anticipated by Sas et al. (EP 389035 A1) for reasons of record stated in the Office Actions dated October 2, 2002.

Sas et al. discloses a pharmaceutical composition comprising highly pure (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one (tibolone). See abstract and Examples 1-8. Sas et al. also discloses a dosage unit comprising a pharmaceutically suitable solid carrier and the 97.2% pure (7α, 7α)-17-hydroxy-7-

methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one in an amount of less than 2.50 mg (see Example 6, form I in an amount of 2.5 mg obtained in example 2 having purity 97.2%). Thus, Sas et al. anticipates claims 1-3, 7 and 9.

Applicant's remarks filed on March 31, 2003 in Paper No. 16 with respect to this rejection of claims 1-3, 7, and 9 made under 35 U.S.C. 102(b) in the previous Office Action have been fully considered and but are not deemed persuasive to render the claimed invention patentable over the prior art as discussed below.

Applicant arguments regarding the two crystal forms, "Form 1" and "Form 2", of (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, are not found convincing, since the instant claims are not limited to any crystal forms of the instant compound.

Again Applicant argues that the presently claimed invention is not anticipated by Sas because the instant composition of (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one comprising (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one, the impurity, in an amount less than 0.5%, 0.25%, or 0.1% by weight whereas Sas is silent about the presence of any impurities in the composition. However, as discussed in the previous Office Actions (October 2, 2002 and February 26, 2002) the expression "*less than* 0.5%, 0.25%, or 0.1% by weight" in the instant claims is seen to merely limit the claims to any amount less than 0.5%, 0.25%, or 0.1% by weight including 0%. Thus, the composition of Sas comprising 0% by weight of impurity herein is within the instant claim.

Applicant assertion that the rejection was based on the inherency. Contrary to Applicant's assertion, the rejection is not based on inherency. As discussed above, the claimed composition clearly reads on the Sas' teachings.

Thus, claims 1-3, 7 and 9 is anticipated by Sas.

Therefore, said rejection is adhered to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sas et al. and Van Vliet et al. for reasons of record stated in the Office Actions dated October 2, 2002.

Sas et al. teaches a process for preparing the high pure (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one comprising aging crystal of (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one (seed crystals) in the presence of water for one hour. Sas et al. also teaches the steps of the process herein such as pouring out the solution in water with small amount of pyridine which makes the solution slightly alkaline and washing the crystals with water and small amount of pyridine which makes the solution slightly alkaline. See Examples 1-4.

Vliet et al. teaches the last step of synthesis of (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one: reacting (7α, 7α)-3,3-dimthoxy-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one in an organic solvent with aqueous oxalic acid (a weak acidic aqueous solution). See page 112 the last line of the 2nd paragraph to the first line of the 1st paragraph. Vliet et al. also teaches that the instant impurity of (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-**4-en**-20-yn-3-one, Compound 21, is present with the desired product, (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, Compound 4, in a composition with less than 1%, isolated and identified by ^{1}H NMR, IR and UV (see page 113 the 1st paragraph of the right column).

The prior art does not expressly disclose that the step of the process herein for aging crystals lasts for at least 24 hours or 3-6 days and pouring out the solution in slight alkaline water and washing the crystals with slight alkaline water.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to optimize the time period for aging crystals to at least 24 hours or 3-6 days and to pour out the solution in slight alkaline water and to wash the crystals with slight alkaline water.

One having ordinary skill in the art at the time the invention was made would have been motivated to optimize the time period for aging crystals to at least 24 hours or 3-6 days because the optimization of the time period for aging crystals to longer period of time in order to obtain more desirable crystals, e.g. highly pure or desired polymorphous forms, is considered well within the skill of artisan. The book "Modern Experimental Organic Chemistry" by Roberts et al. (PTO-1449 March 31, 2003) clearly

supports the examiner's position herein since crystallization and recrystallization by optimizing variables, e.g., time, solvents, and temperature, are well within the skill of artisan (see page 67-75).

Additionally, one having ordinary skill in the art at the time the invention was made would have been motivated to pour out the solution in slight alkaline water and to wash the crystals with slight alkaline water. As discussed above, the steps including pouring out the solution in slight alkaline water and washing the crystals with slight alkaline water are a **conventional** to a skilled artisan, involving merely routine skill in the art, especially Sas has disclosed the steps herein, pouring out the solution in water with small amount of pyridine which makes the solution slightly alkaline and washing the crystals with water and small amount of pyridine which makes the solution slightly alkaline. Vliet et al. also teaches that an organic solvent with aqueous oxalic acid (a weak acidic aqueous solution) was utilized in the last step of synthesis of (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one while the instant purity compound is known to be present therein, one of ordinary skill in the art would reasonably employ slight alkaline water to neutralize the final product mixture in order to purify the desired product.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's remarks filed on March 31, 2003 in Paper No. 16 with respect to this rejection of claims 4-6 made under 35 U.S.C. 103(a) in the previous Office Action have been fully considered and but are not deemed persuasive to remove the rejection. These remarks are believed to be adequately addressed by the obvious rejection presented above.

Again Applicants' argument that Sas does not teach or suggest that the instant impurity is present in an amount less than 0.5% by weight is not found convincing. As discussed above or in the previous Office Action, the expression "less than 0.5% by weight" in the instant claims is seen to merely limit the claims to any amount less than 0.5% by weight. Thus, the instant claims clearly read on the teachings of Sas.

Van Vliet et al. has been cited by the examiner primarily for its teaching that the instant impurity, (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is known to be present (i.e., less than 1%) in the final product of (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one due to the last step of synthesis under weakly acidic conditions in aqueous solution. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 SPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

Therefore, motivation to combine the teachings of the prior art cited herein to make the present invention is seen. The claimed invention is clearly obvious in view of the prior art.

For the above stated reasons, the claimed invention is clearly obvious in view of the prior art. Therefore, said rejection is adhered to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-11 and 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sas et al. (EP 389035 A1) and Van Vliet et al. in view of de Haan (EP 0707848, PTO1449 submitted March 15, 2001).

The same disclosures of Sas et al. and Van Vliet et al. have been discussed above (see supra page 5-6).

Sas et al. does not expressly disclose that the dosage unit comprises pure (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount of 1.25 mg, 0.625 mg or less and the impurity, (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one, in an amount of 5%, 3% 2% or less by weight. Sas et al. does not also expressly disclose that the shelf life period of these compositions herein is 6 months, 1 year, 1.5 years and 2 years. Sas et al. does not expressly disclose the employment well known wet-granulation methods to make the granulate herein containing water in a range of 5.5-7%.

De Haan discloses processes making low dosages of active including the instant compound 7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one (also known as Org OD-14) employing well known wet-granulation methods (according to Remington's Pharmaceutical Sciences, 18th ed) and those dosages containing small amounts of water from 1.20-4.95 mg (see page 3-6).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to prepare the compositions herein comprising pure (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount of 1.25 mg, 0.625 mg or less and the impurity, (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one, in an amount of 5%, 3% 2% or less by weight and to expect the shelf life of these compositions to be 6 months, 1 year, 1.5 years and 2 years, and employ well known wet-granulation methods to make the granulate herein containing water in a range of 5.5-7%.

One having ordinary skill in the art at the time the invention was made would have been motivated to prepare the compositions herein comprising pure (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount of 1.25 mg, 0.625 mg or less and the impurity, (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one, in an amount of 5%, 3% 2% or less by weight since the compositions comprising pure (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount of less than 2.50 mg are known according to Sas et al. Therefore, one of ordinary skill in the art would have found it obvious to prepare the compositions herein comprising pure (7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount of 1.25

mg, 0.625 mg or less because the optimization of amounts of active agents to be administered is considered well within the skill of artisan, involving merely routine skill in the art.

Moreover, wet-granulation methods (according to Remington's Pharmaceutical Sciences, 18th ed) are well known processes making granulates incorporated water in small amounts. Low dosages of active including the instant compound 7α, 7α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one (also known as Org OD-14) containing small amounts of water from 1.20-4.95 mg (see page 3-6) are known according De Haan. Therefore, one of ordinary skill in the art would have found it obvious to employ these known wet-granulation methods to make granulates herein.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Additionally, the shelf lives herein of the compositions are expected since they are the inherent property of the compositions herein, not considered to be a limitation to a composition.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's remarks filed on March 31, 2003 in Paper No. 16 with respect to this rejection of claims 10-18 made under 35 U.S.C. 103(a) have been fully considered and but are not deemed persuasive to remove the rejection. These remarks are believed to be adequately addressed by the obvious rejection presented above.

Additionally, the declaration herein under 37 CFR 1.132 has been considered but is ineffective to overcome the 103(a) rejections herein since the declaration merely presents statements or conclusion regarding the ^{1}H and ^{13}C NMR spectra (not actual the ^{1}H and ^{13}C NMR spectra) of the instant compound and its structural isomer (double migration to position 4) which are already known in the art because these compounds are known in the art in 1986 according to Van Vliet et al. Moreover, obtaining ^{1}H and ^{13}C NMR spectra of known compounds or identify their purity by NMR is considered well within one of ordinary skill in the art, e.g., an organic chemist.

As discussed in the previous Office Action, Applicant's examples 1-6 in the specification at pages 6-9 have been fully considered with respect to the nonobviousness and/or unexpected results of the claimed invention but are not deemed persuasive. Applicant's remarks regarding the comparison with prior art are not found persuasive since the results herein, e.g. the self lives, are clearly expected and not unexpected based on the cited prior art, i.e., the method in Sas has provided a much better stability of the instant compound, e.g., the shelf-life, even under changing storage conditions is notably improved (see Sas page 2 lines 39-40). Therefore, the results on the preparation of the compositions herein and their storage time are expected as taught and suggested by the cited prior art herein. Expected beneficial results are evidence of obviousness. See MPEP § 716.02(c). Therefore, the evidence presented in specification herein is not seen to support the nonobviousness of the instant claimed invention over the prior art.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (703) 305-1008. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
June 9, 2003

SREENI PADMANABHAN
PRIMARY EXAMINER
(SPE|1617) 6|16|03